UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

CHR. HANSEN HMO GMBH, *Plaintiff and Counterclaim-Defendant*, v. GLYCOSYN LLC, *Defendant and Counterclaim-Plaintiff*, v. ABBOTT LABORATORIES, *Counterclaim-Defendant*.	C.A. No. 1:22-cv-11090-NMG **JURY TRIAL DEMANDED**

DEFENDANT AND COUNTERCLAIM-PLAINTIFF GLYCOSYN LLC'S
INITIAL CLAIM CONSTRUCTION BRIEF

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Glycosyn LLC ("Glycosyn") submits this Initial Claim Construction Brief for U.S. Patent No. 9,970,018 (the "'018 patent").

I. INTRODUCTION

This case is about infant formula enhanced with oligosaccharides (small sugars) found naturally in human milk. These human milk oligosaccharides ("HMOs") serve critical roles in the establishment of a healthy gut microbiome, in the prevention of disease, and in immune function. '018 patent col. 1 ll. 37-39. The '018 patent claims methods for producing these HMOs using bacteria that are genetically engineered to, among other things, make low levels of an enzyme called β-galactosidase. Abbott adds HMOs to its premium line of infant formula that have been found to infringe the '018 patent by both the International Trade Commission ("ITC") and the Court of Appeals for the Federal Circuit. Surprisingly, Abbott and Chr. Hansen now take ***the exact same position*** Chr. Hansen took at the ITC, which already resulted in a finding of infringement. *See Jennewein Biotechnologie GMBH v. ITC*, No. 2020-2220, 2021 U.S. App. LEXIS 28200, at *3-4 (Fed. Cir. Sept. 17, 2021) (acknowledging and rejecting Chr. Hansen's position related to the claim term "β-galactosidase activity"); *In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2019 WL 5677974, at *28, *31 (U.S.I.T.C. Sept. 9, 2019) (Initial Determination) (acknowledging Chr. Hansen's position regarding "β-galactosidase gene" and still finding infringement).

Glycosyn was tempted to dispense with this entire *Markman* process by simply agreeing to Abbott and Chr. Hansen's constructions, and then moving for summary judgment of infringement based in the ITC's factual record, but their proposed constructions are just too problematic. They are fundamentally incorrect as a matter of claim construction law, litigation inspired, and could be used

to confuse the jury. Furthermore, the parties' real dispute appears to be less about claim meaning and more about how to apply the facts to the claims.

For example, it is a fact that Chr. Hansen's bacterial strain #1540 contains all the DNA necessary to make β-galactosidase and does indeed make β-galactosidase. But Chr. Hansen inserts the β-galactosidase gene into its bacteria in two pieces. Thus, Abbott and Chr. Hansen construe the claim term "gene" to mean "a single…[contiguous[1]] sequence of DNA." But, the words "single," "contiguous," and "sequence" are found nowhere in the claims, and there is nothing in the specification or the prosecution history that even suggests that "gene" should be defined this way. What is really at issue here is whether Chr. Hansen infringes literally or under the doctrine of equivalents. As the ITC found, even if "gene" is construed to be a "single contiguous sequence of DNA" the #1540 strain still infringes under the doctrine of equivalents. However, the jury should not have to grapple with the doctrine of equivalents when nothing about the claim term "gene" requires a "single contiguous sequence" of DNA.

With respect to the claimed "level of β-galactosidase activity," all parties agree that the '018 patent defines β-galactosidase activity in terms of "Miller Units" defined by the "Miller" protocol. The fact is that performing the Miller protocol on the #1540 strain results in Miller Units in the

[1] Glycosyn understands that Abbott's and Chr. Hansen's addition of "single" to their construction is equivalent to "contiguous." That is, under their construction, the exogenous functional β-galactosidase gene must be a single, contiguous sequence of DNA, and a gene consisting of two separate sequences with intervening DNA would not satisfy this limitation. The nature of the parties' dispute became clear two weeks before the parties' opening briefs were due when Glycosyn offered the following construction as a compromise: "a functional sequence of contiguous or non-contiguous DNA, originating outside the E. Coli bacterium, that encodes a working β-galactosidase enzyme." The only difference between this construction and Abbott's and Chr. Hansen's construction is the deletion of "single" and insertion of "contiguous or non-contiguous." Abbott and Chr. Hansen did not agree to Glycosyn's compromise construction and instead proposed that the parties agree to the ITC's construction. Glycosyn rejected this proposal because the ITC's construction leaves the dispute unresolved, and the Court should resolve that dispute. *See O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1360 (Fed. Cir. 2008).

claimed range. When Chr. Hansen learned this, they tried modifying the Miller protocol to evade infringement. They justified the improper changes using the pretext of identifying activity "attributable to the…β-galactosidase gene." This concept now finds itself in their proposed claim construction. The ITC and Federal Circuit already rejected this. *See Jennewein Biotechnologie GMBH v. ITC*, No. 2020-2220, 2021 U.S. App. LEXIS 28200, at *15. Abbott and Chr. Hansen's erroneous construction could allow them to modify the Miller protocol in any number of ways, or suggest to the jury that Glycosyn has additional burdens that are found nowhere in the claims.

Glycosyn's construction, on the other hand, will help clarify the plain meaning of the claim terms. Simply, if a company puts an exogenous functional β-galactosidase gene into a bacterial strain, and then performs the Miller protocol on the strain and gets results in the claimed range, the company practices this claim element.

II. BACKGROUND

A short primer on relevant aspects of sugar chemistry and bioengineering may be useful. Technical references, and a more thorough background, can be located in the Declaration of Kristala L. Jones Prather, Professor of Chemical Engineering at MIT, filed simultaneously herewith.

A. The Chemistry and Structure of Sugars

Sugars are carbohydrates. As the name implies, they are made up of carbon (C), along with a 2:1 ratio of hydrogen (H) and oxygen (O) like in water (H_2O). Biochemists call sugars "saccharides" and typically give them names that end with –ose. Simple sugars, such as glucose, contain a single saccharide molecule and are called monosaccharides. Monosaccharides can be linked to form disaccharides (two linked) and oligosaccharides (three to ten linked). *See* Ex. 33 (Declaration of Dr. Kristala L. Jones Prather, "Prather Decl.") ¶30; Ex. 2 (Lodish *et al.*, Molecular Cell Biology, 6th ed. (2008)) at GLY-ITC1120_0122273. The HMOs at issue in this case are made up of the same three

monosaccharides: glucose, galactose and fucose. *See* Prather Decl. ¶31; Ex. 3 (Tien Nguyen, Synthesizing Mother's Milk, Chemical & Engineering News, 26-29 (July 2, 2018)) at GLY-ITC1120_0026825; Ex. 2 (Lodish) at GLY-ITC1120_0122272 - GLY-ITC1120_0122273. These monosaccharides are shown in Figure 1 in two structural forms, and are also depicted by a blue circle, a yellow circle, and a red triangle, respectively. *Id.*

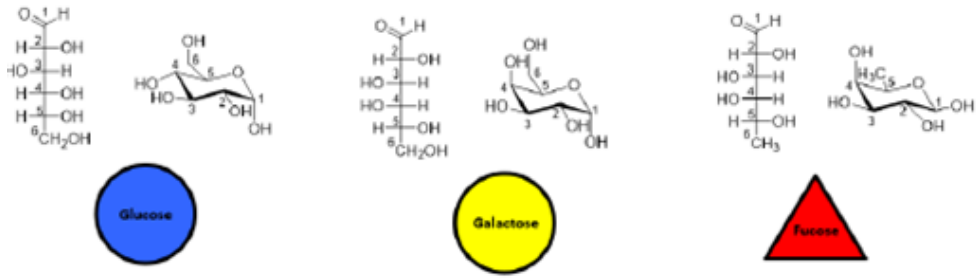

Figure 1: Depiction of glucose, galactose, and fucose (Prather Decl. ¶31)

The claims of the '018 patent are directed to "fucosylated oligosaccharide[s]" made in genetically engineered *E. coli* bacteria. *See* '018 patent at Claim 1. One example of a fucosylated oligosaccharide is 2′-fucosyllactose (2′-FL). As its chemical name suggests, 2′-FL is made by bonding fucose to lactose (a disaccharide consisting of galactose and glucose) as shown in Figure 2.

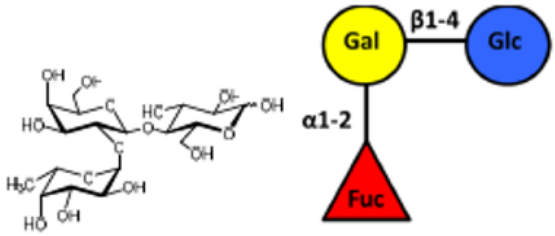

Figure 2: Depiction of 2′-FL (Prather Decl. ¶35)

B. Bioengineering Bacteria To Make Fucosylated Oligosaccharides

Bioengineering involves manipulating an organism's DNA by adding and subtracting genes. *See* Prather Decl. ¶51. A gene contains the molecular "code" for producing functional biological molecules, such as proteins. *Id.* ¶40. When a cell makes proteins, a copy of the DNA that encodes

that protein is transcribed into RNA, which is then translated into a chain of amino acids known as a polypeptide, which can then fold into a three-dimensional structure called a protein. Prather Decl. ¶43. Proteins that catalyze a chemical reaction are called an enzymes. *Id.* ¶44; Ex. 2 (Lodish) at GLY-ITC1120_0122305 - GLY-ITC1120_0122313. Enzymes can either cause two molecules to come together into one piece, or they can break a molecule into two or more pieces. Prather Decl. ¶44.

A relevant example of an enzyme that joins molecules is fucosyltransferase, which joins a fucose molecule to a lactose molecule. *Id.* ¶46. Different fucosyltransferases join fucose to lactose in different ways to yield different fucosylated oligosaccharides such as 2′-FL or 3-FL (2′ and 3 identify where the fucose is added). *Id.* ¶47. Exemplary reactions for 2′-FL and 3-FL are shown below:

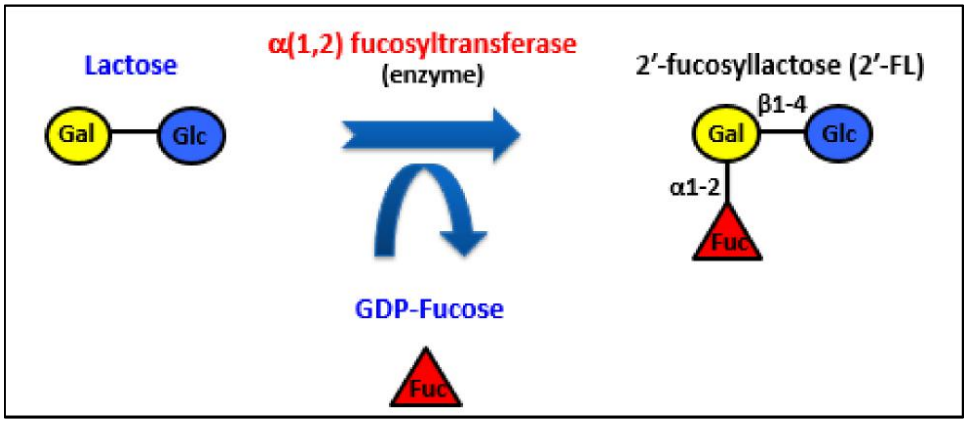

Figure 3: Addition of Fucose to Lactose by α(1,2) fucosyltransferase to Yield 2′-FL (Prather Decl. ¶46)

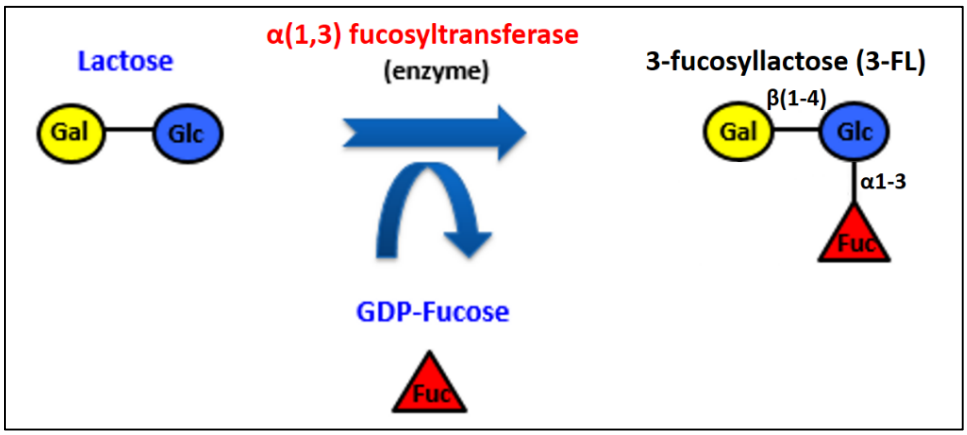

Figure 4: Addition of Fucose to Lactose by α(1,3) fucosyltransferase to Yield 3-FL (Prather Decl. ¶47)

To enable a bacterium to perform this synthesis, the bacterium is genetically manipulated to: (1) increase the intracellular guanosine diphosphate (GDP)-fucose pool; (2) increase the intracellular lactose pool; and (3) add a fucosyltransferase that will bind a fucose to the lactose and thus form a fucosylated oligosaccharide such as 2′-FL. '018 patent col. 5 ll. 1-5.

A relevant example of an enzyme that breaks one molecule into two parts is β-galactosidase, which breaks down lactose into its constituent parts, galactose and glucose. Prather Decl. ¶45.

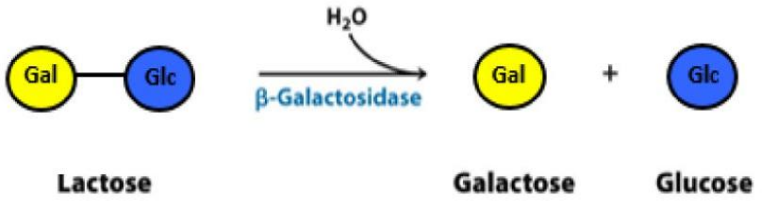

Figure 5: Depiction of β-galactosidase Breaking Down Lactose (Prather Decl. ¶45)

β-galactosidase and fucosyltransferase work directly against each other, as β-galactosidase destroys the lactose that the fucosyltransferase needs to create fucosylated oligosaccharides. '018 patent col. 16 ll. 37-49. Therefore, to increase the intracellular lactose pool, the engineered bacterium of the claimed method is modified to delete the endogenous β-galactosidase gene (which is called *lacZ*). *Id.* at col. 5 ll. 13-14. This increased lactose pool ensures the availability of lactose for the desired fucosyltransferase reaction. *Id.* at col. 5 ll. 16-19.

While scientists discovered that elimination of native, "wild type" levels of β-galactosidase was advantageous to the production of bioengineered fucosyllactose, they also discovered that complete elimination of β-galactosidase can cause problems. One problem is that "complete elimination of β-galactosidase activity creates purification issues at the end of the manufacturing process." *Jennewein Biotechnologie GMBH v. ITC*, No. 2020-2220, 2021 U.S. App. LEXIS 28200,

at *3-4 (Fed. Cir. Sept. 17, 2021) (citing '018 patent at col. 7 ll. 37-45). To overcome such problems, the engineered *E. coli* of the claimed method includes an exogenous functional β-galactosidase gene "to direct the expression of a low, but detectable level of β-galactosidase activity." '018 patent col. 6 ll. 7-11. The result is an engineered bacterium comprising a very low level of β-galactosidase activity, between 0.05 and 200 Miller units. "Surprisingly, it was determined that microorganisms that produce less β-galactosidase activity than a microorganism with a non-defective *lacZ* gene are the best producers of 2'-FL (as compared to microorganisms that express normal levels of β-galactosidase or express no β-galactosidase.)." Ex. 4 (U.S. Patent No. 9,944,965) at col. 7 ll. 11-15.

C. β-Galactosidase and Alpha Complementation

β-galactosidase is unusual in a number of ways that are relevant to this case. First, the *lacZ* gene encodes a monomer (one LacZ[2] peptide), but β-galactosidase is a tetramer (four LacZ peptides). When four LacZ monomers are present, they spontaneously assemble into an active tetrameric β-galactosidase enzyme. Prather Decl. ¶50. Second, the *lacZ* gene can be broken into two parts, called *lacZα* and *lacZΩ*, and still work. *Id.* ¶49. That is, *lacZα* contains the genetic code for one part of the LacZ peptide, while *lacZΩ* encodes the other part. *Id.* If both LacZα and LacZΩ peptides are present, they spontaneously assemble into a full-length LacZ peptide, which then spontaneously assembles into a working tetrameric β-galactosidase enzyme. *Id.* Thus, when sufficient amounts of the LacZα and LacZΩ peptides are present, they spontaneously assemble into an active β galactosidase enzyme. This concept is known as "alpha-complementation" and is depicted below. *Id.* ¶¶49-50.

[2] Persons of skill in the art use the following nomenclature to distinguish between genes and the peptides they encode: genes are written in *italics* with a lower-case first letter (e.g., *lacZ*)—while peptides produced from genes are not italicized and start with a capital letter (e.g., LacZ, LacZα, LacZΩ). Prather Decl. ¶49 n.2.

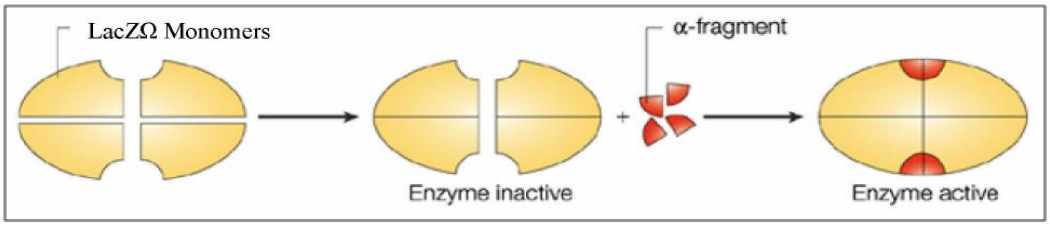

Figure 6: Alpha Complementation in the β-galactosidase Homotetramer Prather Decl. ¶50

Once the working tetrameric β-galactosidase enzyme assembles, β-galactosidase activity can be measured using the Miller protocol. *See* '018 patent col. 7 ll. 30-37; Ex. 32 (Miller, J.H., Experiments in Molecular Genetics (Cold Spring Harbor Lab. 1972) at 352-355). As the Federal Circuit noted, "the Miller protocol includes the following steps: (1) taking a sample from a culture of growing bacterial cells; (2) permeabilizing the bacterial cells with chloroform or toluene; (3) incubating the permeabilized bacterial cells with onitrophenyl-β-D-galactoside (ONPG), a colorless compound specifically recognized and cleaved by β-galactosidase to produce a yellow product; and (4) measuring with a spectrophotometer the amount of yellow color that develops over a set period of time. The values recorded by the spectrophotometer are then entered into a mathematical equation to provide the level of β-galactosidase activity in Miller units." *Jennewein Biotechnologie GMBH v. ITC*, 2021 U.S. App. LEXIS 28200, at *4, n.1.

III. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art for purposes of this case would typically have a Ph.D. in molecular biology, biochemistry, biological or chemical engineering, or an equivalent field, and 1-2 years of experience working with *E. coli* bacteria or related systems. Or such a person could have a lower level degree (e.g., a M.A.) in a similar field to those listed above, but a greater amount of relevant working experience (e.g., 5-6 years of experience working with *E. coli* bacteria or related systems). Prather Decl. ¶¶22-24.

IV. LEGAL PRINCIPLES OF CLAIM CONSTRUCTION

A patent infringement analysis entails two steps. "The first step is determining the meaning and scope of the patent claims asserted to be infringed. The second step is comparing the properly construed claims to the device accused of infringing." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc) (internal citations omitted), aff'd, 517 U.S. 370 (1996). The first step, known as claim construction, is an issue of law for the court to decide. *Id.* at 979. The second step is determined by the finder of fact. *Id*.

In construing the terms of a patent, "the words of a claim are generally given their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) ("Phillips") (en banc) (internal quotation omitted). Thus, "[t]he Court's responsibility in construing claims is to determine the meaning of claim terms as they would be understood by persons of ordinary skill in the relevant art." *Milliman, Inc. v. Gradient A.I. Corp.*, No. 21-10865-NMG, 2023 U.S. Dist. LEXIS 9172, at *4 (D. Mass. Jan. 19, 2023) (citing *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1267 (Fed. Cir. 2001)). "The meanings of the terms are initially discerned from three sources of intrinsic evidence: 1) the claims themselves, 2) the patent specification and 3) the prosecution history of the patent." *Milliman*, 2023 U.S. Dist. LEXIS 9172 at *4-5 (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582-83 (Fed. Cir. 1996)). "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, 415 F.3d at 1316 (*quoting Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

There are only two exceptions to the general rule that claims are given their ordinary and customary meaning: lexicography and disavowal. *Thorner v. Sony Comp. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). "To act as its own lexicographer, a patentee must 'clearly set forth a

definition of the disputed claim term' other than its plain and ordinary meaning. *Id*. (quoting *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). "The standard for disavowal of claim scope is similarly exacting." *Id*. at 1336. Disavowal requires "a clear and unmistakable disclaimer." *Id*. at 1366-67. It is "not enough that the only embodiments, or all of the embodiments, contain a particular limitation. We do not read limitations from the specification into claims; we do not redefine words. Only the patentee can do that." *Id*. Claim construction is an important exercise for a district court to perform, because "[i]n the end, claim construction must result in a phraseology that can be taught to a jury of lay people." *Control Res., Inc. v. Delta Elecs., Inc.*, 133 F. Supp. 2d 121, 127 (D. Mass. 2001).

V. THE CLAIM TERMS AT ISSUE

A. "[an] exogenous functional β-galactosidase gene"

The parties agree that "exogenous" means "originating outside the organism" and that a "functional β-galactosidase gene" must encode a working β-galactosidase enzyme. Still, the parties' disagree about what a "gene" is, and have proposed the following constructions:

Term	Glycosyn's Construction	Abbott's & Chr. Hansen's Construction
"[an] exogenous functional β-galactosidase gene" ('018 patent claims 1, 8, 23, 24)	Plain and ordinary meaning, *i.e.*, "contiguous or non-contiguous DNA originating outside the *E. coli* bacterium that encodes for a working β-galactosidase enzyme"	"a single functional sequence of DNA, originating outside the *E. coli* bacterium, that encodes a working β-galactosidase enzyme"

Glycosyn contends that if a cell has DNA that encodes a working β-galactosidase enzyme, it has a β-galactosidase ***gene***. Abbott and Chr. Hansen contend that, even if a cell has DNA that encodes a working β-galactosidase enzyme, it does not have a β-galactosidase ***gene*** unless that DNA is organized in a "single functional [contiguous] sequence." Under either construction, Abbott and Chr.

Hansen have already been found to infringe this claim element. This dispute merely determines whether the infringement is literal or under the doctrine of equivalents.

In its *Markman* order, the ITC held that "'functional … β-galactosidase gene' is hereby construed as '**a functional sequence of DNA that encodes β-galactosidase**.'" *In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2018 WL 6837945, at *22-23 (U.S.I.T.C. Dec. 18, 2018) (Order No. 22: Construing the Terms of the Asserted Claims of the Patents at Issue) (emphasis in original). No party had proposed that "sequence" be part of the construction, and they continued to disagree about what a "sequence of DNA" meant. Chr. Hansen, who had inserted an exogenous β-galactosidase gene in two parts (*lacZα* and *lacZΩ*) instead of one *(lacZ)*, argued that the construction required a single sequence of DNA. Glycosyn contended that regardless of how many parts the β-galactosidase gene was broken into, the entire "sequence of DNA" that encodes β-galactosidase was literally in Chr. Hansen's bacteria. In the meantime, the case was transferred to a new administrative law judge ("ALJ"), who applied the previous ALJ's construction and ultimately held that "Jennewein's Accused Strains do not literally infringe 'an exogenous functional β-galactosidase gene' ***because they lack a single sequence of DNA*** which functions to create a β-galactosidase gene… [however] ***I find the lacZa and lacZΩ genes are equivalent*** to 'an exogenous functional β-galactosidase gene.'" *In the Matter of Certain Hum. Milk Oligosaccharides & Methods of Producing the Same*, Inv. No. 337-TA-1120, 2019 WL 5677974, at *28, *31 (U.S.I.T.C. Sept. 9, 2019) (Initial Determination).

The reason the ITC held that a single contiguous gene was required for literal infringement is because the "plain and ordinary meaning of '***sequence***' does imply contiguity." *Id*. at *28 (emphasis added). The word "sequence," however, is found nowhere in the claims. The ITC thus applied its own construction in a way that required a "contiguous sequence of DNA." But this understanding is

contrary to the basics of the field of art. A gene is merely a "basic unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify physical and biological traits." Ex. 5 (https://www.genome.gov/genetics-glossary/Gene) at 2; *see also* Ex. 6 (https://dictionary.cambridge.org/us/dictionary/english/gene) at 1 (defining gene as "a part of the DNA in a cell that controls the physical development, behavior, etc. of an individual plant or animal and is passed on from its parents."). Thus, the ITC's application of its construction, and the construction proposed by Abbott and Chr. Hansen now, is too narrow. The Court should adopt Glycosyn's proposed construction.

Turning first to the claims, they emphasize the ***functionality*** of the claimed gene, not a specific structure (*i.e.*, single sequence) of the DNA. Take, for example, claim limitation 1(ii):

> an exogenous functional β-galactosidase gene comprising a detectable level of β-galactosidase activity that is reduced compared to that of a wild-type E. coli bacterium, wherein the level of β-galactosidase activity comprises between 0.05 and 200 units

'018 patent, claim 1. The focus of this limitation is the functional result: the bacterium must have a level of β-galactosidase activity that comprises between 0.05 and 200 units. Nothing else is stated or required. This language reflects the patentee's careful choice to secure broad claims covering a variety of functional β-galactosidase genes with a variety of different DNA sequences, as supported by the patent specification. *See id.* The patentee envisioned the invention as covering a variety of β-galactosidase genes—native and recombinant (genetically modified) and from "any number" of organisms. *See id.* at col. 6 ll. 7-11 ("[The methods of the invention are] achieved by utilizing a functional β-galactosidase (e.g., lacZ) gene insert carefully engineered to direct the expression of a low, but detectable level of β-galactosidase activity in an otherwise β-galactosidase negative host cell."), col. 7 ll. 22-45 (describing the activity of the disclosed functional β-galactosidase gene and listing as examples recombinant *E. coli* lacZ genes or β-galactosidase genes "from any number of

other organisms"). The patentee did not limit the meaning of "gene," with words like "contiguous" or "sequence." *See generally* '018 patent.

Similarly, the extrinsic record contradicts Abbott and Chr. Hansen's narrowing construction. For example, genes that include "introns" are another example of non-contiguous DNA that is still able to produce a functional enzyme. Protein-producing genes in many organisms have internal sequences of DNA, introns, that do not encode for the resulting functional protein. Prather Decl. ¶¶42, 79; Ex. 5 (https://www.genome.gov/genetics-glossary/Gene). The presence of the introns results in multiple non-contiguous sequences of DNA that together are known as genes and encode for the functional protein. Prather Decl. ¶¶42, 79; Ex. 5 (https://www.genome.gov/genetics-glossary/Gene).The net effect is that there is more than just "contiguous" DNA than actually encodes a given functional gene product, or protein. Put another way, the DNA encoding an enzyme may be "non-contiguous" (and indeed often is non-contiguous) and still be able to produce a working enzyme.

Yet another example of non-contiguous DNA being capable of producing a functional enzyme is the LacZ gene itself. As discussed above, the *LacZ* gene, which encodes for β-galactosidase, can be separated into two sequences of DNA, *LacZα* and *LacZΩ*. Prather Decl. ¶¶49, 74. Each fragment encodes for a piece, or "peptide" of the functional β-galactosidase enzyme. *Id.* When both peptides are present in a bacterium, they spontaneously assemble into a full-length LacZ monomer peptide. *Id.* This spontaneous assembly of peptides from non-contiguous DNA is known as "alpha-complementation." *Id.* In turn, four full-length LacZ monomer peptides also spontaneously assemble into a functional β-galactosidase enzyme. *Id.* Again, despite being non-contiguous DNA, LacZα and LacZΩ comprise the entire sequence of DNA that produces a working β-galactosidase enzyme.

Thus, for the purposes of the claimed invention, it does not matter whether the DNA comprising the β-galactosidase gene is contiguous or non-contiguous. A POSITA at the time of the invention would have understood that non-contiguous DNA (*i.e.*, *LacZα* and *LacZΩ*), as a whole, is a functional β-galactosidase gene encoding for a working β-galactosidase enzyme. *See* Prather Decl. ¶¶75-80.

Contrary to the ordinary meaning of the term "functional … gene," and contrary to the intrinsic and extrinsic evidence, Abbott and Chr. Hansen propose a narrowing construction that excludes from the scope of the claim non-contiguous DNA that encodes for a working β-galactosidase enzyme. There are only two exceptions to the general rule that claims are given their ordinary and customary meaning as understood by a person of ordinary skill in the art when read in the context of the intrinsic record: lexicography and disavowal. *Thorner v. Sony Comp. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). The standards for finding lexicography and/or disavowal are "exacting." *Id.* at 1366 ("To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning" and "clearly express an intent to redefine the term," and disavowal requires "a clear and unmistakable disclaimer."). Nothing in the intrinsic record meets these exacting standards—the patentee neither used definitional language nor make any clear and unmistakable disclaimers that excluded non-contiguous DNA from the scope of "[an] exogenous functional β-galactosidase gene."

Abbott and Chr. Hansen can point to no evidence indicating lexicography and disavowal. On the contrary, the overwhelming intrinsic and extrinsic evidence demonstrates that "[an] exogenous functional β-galactosidase gene" should be afforded its plain and ordinary meaning, *i.e.*, "contiguous or non-contiguous DNA originating outside the *E. coli* bacterium that encodes for a working β-galactosidase enzyme."

B. "the level of β-galactosidase activity comprises between 0.05 and [200 units / 5 units /4 units / 3 units/ 2 units]"

The parties agree in part and disagree in part on the proper claim construction of the term "*the level of β-galactosidase activity comprises between 0.05 and [200 units/ 5 units/ 4 units/ 3 units/ 2 units]*." The parties' proposed construction are reproduced below, with italics showing where they agree and bold showing where they disagree:

Term	Glycosyn's Construction	Abbott & Chr. Hansen's Construction
"the level of β-galactosidase activity comprises between 0.05 and 200 units" ('018 patent claims 1, 8, 23, 24)	**"when a culture of the E. Coli bacteria comprising the exogenous functional β-galactosidase gene is assayed using the Miller protocol,** *β-galactosidase activity is measurable at between exactly 0.05 and exactly [200/5/4/3/2] Miller Units, as defined in Miller, J.H., Experiments in Molecular Genetics. Cold Spring Harbor Laboratory (Cold Spring Harbor, N.Y.; 1972) at 352-355*"	"*β-galactosidase activity is measurable at between exactly 0.05 and exactly [200/5/4/3/2] Miller Units, as defined in Miller, J.H., Experiments in Molecular Genetics (Cold Spring Harbor Lab. 1972) at 352-355,* **where the β-galactosidase activity is the β-galactosidase activity attributable to the expression of the exogenous functional β-galactosidase gene only**"

1. "Units" Means "Miller Units"

The parties agree that the term "units" means "Miller Units, as set forth in Miller, J.H., Experiments in Molecular Genetics (Cold Spring Harbor Lab. 1972) at 352-355." The patentee expressly defined "units" this way in the patent's specification. *See* '018 patent at col. 7 ll. 34-37 ("for unit definition see: Miller J H, Laboratory CSH. Experiments in molecular genetics. Cold Spring Harbor Laboratory Cold Spring Harbor, N.Y.; 1972; incorporated herein by reference"); *see also* Ex. 32 (Miller). The is clear patentee lexicography, and must control. *Phillips*, 415 F.3d at 1316 ("[T]he specification may reveal a special definition given to a claim term by the patentee…[i]n such

cases, the inventor's lexicography governs."). Thus, "units" should be construed to mean "Miller Units" as defined in Miller 1972.

This is how the Commission and Federal Circuit construed the term. The Commission held that: "'β-galactosidase activity comprises between 0.05 and [200 units/ 5 units/ 4 units/ 3 units/ 2 units]' is hereby **not found to be indefinite** and construed as '**β-galactosidase activity is measurable at between exactly 0.05 and exactly [200/5/4/3/2] Miller Units, as defined in Miller, J.H., Experiments in Molecular Genetics (Cold Spring Harbor Lab. 1972) at 352-355.**'" *Certain Hum. Milk Oligosaccharides*, 2018 WL 6837945, at *18 (Order No. 22: Construing the Terms of the Asserted Claims of the Patents at Issue) (emphasis in original). The Federal Circuit affirmed the Commission's construction. *Jennewein Biotechnologie GMBH v. ITC*, 2021 U.S. App. LEXIS 28200, at *26 ("…we affirm the Commission's claim construction and its finding of infringement…"); *see also id*. at *21 ("[T]he claim language and intrinsic evidence support the Commission's construction …: [t]he level of 'β-galactosidase activity is measurable at between exactly 0.05 and exactly [200] Miller units, as defined in Miller.'").

2. The Claims Do Not Permit Changes to the Miller Protocol when Determining "Units"

While the Commission's construction is correct, the parties still appear to disagree about how to apply it. Whether this is a disagreement about the term's plain and ordinary meaning or otherwise, the Court should resolve the dispute before the jury hears this case, and in a way that is helpful to the jury. *Milliman*, 2023 U.S. Dist. LEXIS 9172, at *7-8 ("In construing claim terms the Court should also be mindful that "[t]his case will eventually be presented to a lay jury, and therefore, '[i]t is not enough simply to construe the claims so that one skilled in the art will have a definitive meaning. The claims must be translated into plain English so that a jury will understand.") (quoting *Control Res., Inc. v. Delta Elecs., Inc.*, 133 F. Supp. 2d 121, 127 (D. Mass. 2001)).

While not expressly stated in either parties' construction, the real dispute centers on whether it is appropriate to modify the Miller protocol when determining the claimed "units." The ITC and Federal Circuit have already held that it is not. *See Certain Hum. Milk Oligosaccharides*, 2019 WL 5677974 at *33 (Initial Determination) ("The U.S. Patent and Trademark Office issued claims to Glycosyn which ***expressly define the invention's scope in terms of Miller Units*** customized by the Miller protocol. Thus, reliable or not, it is the test to be used—a point [Chr. Hansen] concedes in other portions of its brief") (emphasis added); *id.* ("the test is…whether [Chr. Hansen] 'provides' and '*E. coli* bacterium' which 'comprises' Miller Unit activity within the claimed range ***when put through the procedures outlined in Miller***"); *Jennewein Biotechnologie GMBH v. ITC*, 2021 U.S. App. LEXIS 28200, at *18 ("Glycosyn's testing simply hewed more closely to the Miller protocol, i.e., ***the terms in which the invention is defined***.") (quotations removed, emphasis added).

Nothing in the patent allows changes to the Miller protocol—a point that Chr. Hansen itself repeatedly made during the ITC's *Markman* proceedings. *See* Ex. 7 (Markman Hrg Tr.) at 29:21-23 ("And again, we think that the patent makes it clear that you have to follow the Miller method, not just the calculation."); *id.* at 30:3-13 ("So that's our first point, that when you're looking at Miller, you have to follow the assay…"); *see also Certain Hum. Milk Oligosaccharides*, 2018 WL 6837945, at *14 ("[Chr. Hansen] emphasizes that …, 'units must be measured according to the assay procedures in Miller.'") (quoting Jennewein's reply Markman brief); *see also id.* ("[Chr. Hansen] argues '[d]uring the prosecution…the patentee made clear that units of β-galactosidase activity ***must be measured according to the assay procedures in Miller***' [] and so Glycosyn is now judicially estopped from arguing otherwise now.") (citing Jennewein's initial Markman brief) (emphasis added); Prather Decl. ¶¶66-67.

Chr. Hansen even asked the ITC to include in its construction the phrase "when measured according to the assay procedures described in the Miller textbook" to ensure that the parties measured β-galactosidase activity strictly according to the Miller protocol. *Certain Hum. Milk Oligosaccharides*, 2018 WL 6837945, at *10, *17. The ITC declined to add the requested phrase, but it agreed with the sentiment, holding that the requirement "is already present through the claim's explicit recitation of Miller Units." *Id*. at *17. Thus, both the ITC and Federal Circuit agreed that the claim term "*the level of β-galactosidase activity comprises between 0.05 and [200/5/4/3/2] units*" does not permit changes to the Miller protocol.

Glycosyn's proposed construction therefore best represents the plain and ordinary meaning of the claim term. *See* Prather Decl. ¶¶63-67. Simply stated, "*when a culture off the E. coli bacteria comprising the exogenous functional β-galactosidase gene is assayed using the Miller protocol, β-galactosidase activity is measureable at between exactly 0.05 and [200/5/4/3/2] Miller Units*." This restatement of the plain meaning emphasizes that if a company puts an exogenous functional β-galactosidase gene into a bacterial strain, and then performs the Miller protocol on the strain and gets results in the claimed range, the company practices this claim element.

Conversely, Abbott and Chr. Hansen's construction invites confusion and mischief. For example, after arguing to the ITC that the claims required strict adherence to the Miller protocol, Chr. Hansen then modified the Miller protocol to avoid infringement. Specifically, Chr. Hansen hired a third party to perform the Miller Test on the accused #1540 strain, which they had engineered to include an exogenous β-galactosidase gene (in the form of *lacZα* and *lacZΩ*). *Jennewein Biotechnologie GMBH v. ITC*, 2021 U.S. App. LEXIS 28200, at *17. The test resulted in Miller Units in the claimed range, albeit at the lower end of the range. *Id*.

That result was not good for Chr. Hansen's' non-infringement defense. So, Chr. Hansen had the third party manipulate the Miller protocol by subtracting a negative control strain from the resulting Miller Units. *Id*. Subtracting negative control strains is not a part of the established Miller Test protocol since the Miller protocol already includes negative controls. *See Jennewein Biotechnologie GMBH v. ITC*, 2021 U.S. App. LEXIS 28200, at *15 ("Regardless, the Miller assay specifies several controls to account for any background noise and does not use a negative control strain to do so."); *Certain Hum. Milk Oligosaccharides*, 2019 WL 5677974, at *34 n.3 (Initial Determination); Ex. 32 (Miller) at GLY-ITC1120_0001810 - GLY-ITC1120_0001811; Prather Decl. ¶¶66-67. Chr. Hansen's modified Miller protocol still resulted in units[3] in the claimed range, so the third party suggested that perhaps subtracting different control strains could possibly further lower the results forcing them outside the claims' lower bounds. *Id*. (quoting the third party, who stated "'unfortunately, the Miller activity at your 1540 (30 °C) batch is still above 0.05 after subtracting [a third possible negative control strain],' and 'if we subtract [one of the two previously discussed negative control strains] instead of the [third possible negative control strain] as reference, the value would fall below 0.05'" and citing J.A. 51523-51524[4]). The ITC and Federal Circuit rejected this litigation-inspired manipulation of the Miller protocol. *See id*. at *17-18 (Federal Circuit finding substantial evidence that Chr. Hansen improperly manipulated the Miller Protocol to minimize the measured Miller Units); *see also Certain Hum. Milk Oligosaccharides*, 2019 WL 5677974 at *33 (Initial Determination) ("This [negative control strain] step is indisputably not found in Miller, and, for reasons discussed further below, I do not find it has been shown to be necessary ***or even appropriate***.") (emphasis added).

[3] These units were not technically Miller Units since the Miller Protocol was altered.
[4] Chr. Hansen considers the remaining information in this document to be confidential, so in the interest of keeping the entire Markman record public, we do not produce it here.

Abbott and Chr. Hansen's proposed new construction will again allow them to tinker with the Miller protocol to manipulate results under the pretense of discerning "activity ***attributable*** to the expression of the exogenous functional β-galactosidase gene ***only.***" The Court should reject this attempt. It will not only confuse the jury, but it will also insert words into the claim (and the Miller Test) that are simply not there, and for which no support is provided in the patent specification. For example, in addition to having been rejected by both the ITC and the Federal Circuit, Abbott and Chr. Hansen's proposed construction does not inform the jury how to "attribute" β-galactosidase activity to the inserted gene if not by following the Miller protocol. This could confuse the jury by permitting any number of creative changes to the protocol. *Bose Corp. v. SDI Techs., Inc.*, 828 F. Supp. 2d 415, 424 (D. Mass. 2011), aff'd, 558 F. App'x 1012 (Fed. Cir. 2014) (finding a proposed construction "unnecessarily confusing"); *see also SoClean, Inc. v. Sunset Healthcare Sols., Inc.*, No. 1:20-cv-10351-IT, 2020 U.S. Dist. LEXIS 245517, at *11 (D. Mass. July 31, 2020) ("Far from clarifying the scope of the claim, this construction only serves to confuse the experts, the court, and, likely, the jury.") (*citing Bose Corp.*, 828 F. Supp. 2d at 424).

The '018 patent does not contemplate such changes to the Miller protocol. Nor does any intrinsic or extrinsic evidence instruct how to make these hypothetical modifications. The patent simply tells the reader to perform the Miller test. As Dr. Prather points out, that is more than enough instruction for a person of ordinary skill in the art, as the Miller test has been around far more than a half-century. Prather Decl. ¶¶63-65. Accordingly, Glycosyn's construction should be adopted and Abbott and Chr. Hansen's construction should be rejected.

VI. CONCLUSION

For these reasons, Glycosyn requests that the Court adopt Glycosyn's proposed constructions and specifically reject Abbott and Chr. Hansen's proposed constructions.

Dated: August 24, 2023

Respectfully submitted,

/s/ *Michael C. Newman*

Michael C. Newman (BBO #667520)
mcnewman@mintz.com
Thomas H. Wintner (BBO #667329)
twintner@mintz.com
James Wodarski (BBO #627036)
jwodarski@mintz.com
Michael Renaud (BBO #629783)
mtrenaud@mintz.com
Peter J. Cuomo (BBO #661368)
pjcuomo@mintz.com
Matthew A. Karambelas (BBO #691034)
makarambelas@mintz.com
Courtney Herndon (BBO #693418)
cherndon@mintz.com
Nana Liu (BBO #694201)
NLiu@mintz.com
Williams S. Dixon (BBO #705286)
WSDixon@mintz.com
Simone B. Yhap (BBO #711761)
sbyhap@mintz.com
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO P.C.
One Financial Center
Boston, MA 02111
Phone: (617) 542-6000
Fax: (617) 542-2241

Counsel for Defendant and Counterclaim Plaintiff Glycosyn LLC

CERTIFICATE OF SERVICE

I certify that on August 24, 2023, I caused a true and correct copy of the foregoing to be served via ECF on all counsel of record.

/s/ *Michael C. Newman*
Michael C. Newman